CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

LABELING

ANGELIQ® TABLETS

(Drospirenone and Estradiol)

0.5 mg/1 mg

Rx Only **PRESCRIBING INFORMATION**

WARNING

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia. (See **WARNINGS, Cardiovascular disorders and Dementia**.)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies and WARNINGS, Cardiovascular disorders and Malignant neoplasms, Breast cancer**.)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens alone and during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies, WARNINGS, Dementia and PRECAUTIONS, Geriatric Use**.)

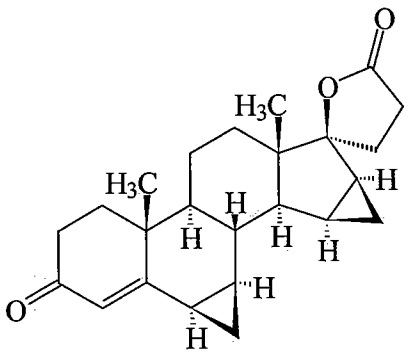
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials, and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

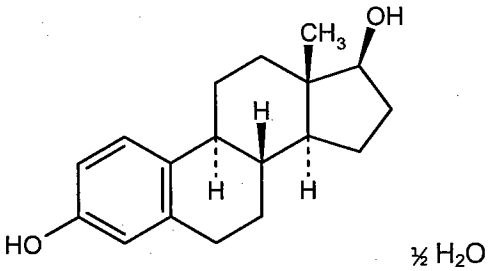
ANGELIQ TABLETS provide a hormone regimen consisting of film coated tablets each containing 0.5 mg of drospirenone and 1 mg of estradiol. The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxylpropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.

Drospirenone, (6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7:15,16]cyclopenta[*a*]phenanthrene-17,2′(5*H*)-furan]-3,5′(2*H*)-dione (CAS) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

Estradiol USP, (Estra–1,3,5(10)–triene–3,17–diol,17β), has a molecular weight of 272.39 and the molecular formula is $C_{18}H_{24}O_2$. The structural formulas are as follows:



Drospirenone



Estradiol ½ H_2O

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol (E2) is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These will vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), through a negative feedback mechanism.

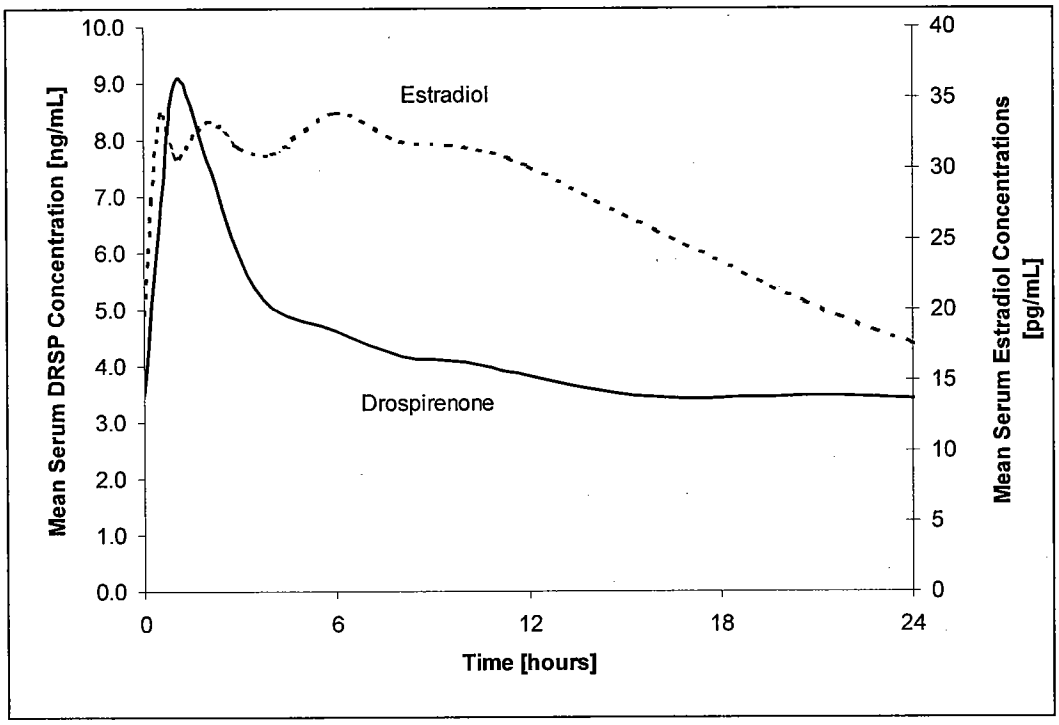
Drospirenone (DRSP) is a synthetic progestin and spironolactone analog with antimineralocorticoid activity. In animals and in vitro, drospirenone has antiandrogenic activity, but no glucocorticoid, antiglucocorticoid, estrogenic, or androgenic activity. Progestins counter estrogenic effects by decreasing the number of nuclear estradiol receptors and suppressing epithelial DNA synthesis in endometrial tissue.

Pharmacokinetics

Absorption: Serum concentrations of DRSP reach peak levels approximately 1 hour after administration of **ANGELIQ** and mean absolute bioavailability of DRSP ranges from 76-85%. Following oral administration, peak serum estradiol concentrations are typically reached 6-8 hours after dosing with **ANGELIQ**. The oral relative bioavailability of estradiol and DRSP following administration of **ANGELIQ** is 107% and 102%, respectively when compared to a combination oral suspension.

The pharmacokinetics of DRSP are dose proportional within the dose range of 0.5-4 mg. Following daily dosing of **ANGELIQ**, steady state DRSP concentrations were observed after 10 days. Mean accumulation ratios for estradiol and DRSP were 1.9 and 2.4, respectively. Mean concentrations at 2 hours for DRSP ranged between 5.9 and 6.7 ng/mL after treatment with ANGELIQ for 365 days. Mean steady state serum DRSP and E2 concentrations are shown in Figure 1, and a summary of primary pharmacokinetic parameters following the administration of 1mg E2/1mg DRSP for 28 days is presented in Table 1.

Figure 1: Mean steady state serum drospirenone and estradiol concentrations following daily oral administration of 1 mg E2/0.5 mg DRSP[1]



[1] DRSP levels are simulated based on data obtained after oral administration of 1 mg DRSP/1 mg Estradiol

Table 1: Mean Steady State Pharmacokinetic Parameters of Tablets Containing Drospirenone (1 mg)* and Estradiol (1 mg)

Drospirenone (Mean** ± SD)					
Dose	**No. of Subjects**	**C_{max} (ng/mL)**	**t_{max} (h) Median (range)**	**AUC(0-24h) (ng•h/mL)**	**$t_{1/2}$ (h)**
1mg E2/1mg DRSP	14	18.3 ± 5.55	1.0 (1.0-2.0)	208 ± 83	42.3 ± 21.3
Estradiol (Mean ± SD)					
Dose	**No. of Subjects**	**C_{max} (pg/mL)**	**t_{max} (h) Median (range)**	**AUC(0-24h) (pg•h/mL)**	**$t_{1/2}$ (h)**
1mg E2/1mg DRSP	14	43.8 ± 10.0	2.5 (0.5-12.0)	665 ± 178	NA
Estrone (Mean ± SD)					
Dose	**No. of Subjects**	**C_{max} (pg/mL)**	**t_{max} (h) Median (range)**	**AUC(0-24h) (pg•h/mL)**	**$t_{1/2}$ (h)**
1mg E2/ 1mgDRSP	14	245 ± 50.6	4.0 (3.0-6.0)	3814 ± 1159	23 ± 6.2

*Angeliq™ contains 0.5 mg DRSP
** arithmetic mean
NA = Not available, C_{max}=Maximum serum concentration, AUC=area under the curve, t_{max}=time of maximum serum concentration, $t_{1/2}$= half-life, SD= standard deviation.

Effect of Food: The effect of food on the absorption and bioavailability of DRSP and E2 have not been investigated following the administration of **ANGELIQ**. However, clinical studies with different formulations containing DRSP or E2 have shown that the bioavailability of both drugs is not affected by concomitant food intake.

Distribution: The mean volume of distribution of DRSP is 4.2 L/kg. DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1%-2% is unbound.

Metabolism: Mean clearance of DRSP is 1.2 mL/min/kg. DRSP is extensively metabolized after oral administration. The 2 main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate, both of which are formed without the involvement of the cytochrome P450 system. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by Cytochrome P450 3A4 (CYP3A4).

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to

estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion: DRSP serum levels are characterized by a terminal elimination half-life of approximately 36-42 hours. Excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38% to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17% to 20% of the metabolites were excreted as glucuronides and sulfates. Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations:

Geriatric*:* No pharmacokinetic studies were conducted in the geriatric population.

Pediatric*:* No pharmacokinetic study for **ANGELIQ** has been conducted in a pediatric population.

Gender*:* **ANGELIQ** is indicated for use in women only.

Race*:* No studies were done to determine the effect of race on the pharmacokinetics of **ANGELIQ**.

Patients with Hepatic Impairment: **ANGELIQ** is contraindicated in patients with hepatic dysfunction **(also see BOLDED WARNING).** The mean exposure to DRSP in women with moderate liver impairment is approximately three times the exposure in women with normal liver function.

Patients with Renal Impairment: **ANGELIQ** is contraindicated in patients with renal insufficiency **(also see BOLDED WARNING).**

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effects of DRSP on serum potassium levels were investigated in female subjects (n = 28, age 30 - 65) with normal renal function (11 patients), and mild (10 patients) and moderate (7 patients) renal impairment. All subjects were on a low potassium diet. During the study 7 subjects continued the use of potassium-sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CLcr 30-50 mL/min) compared to those in the group with normal renal function. Serum DRSP levels in the group with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those in the group with normal renal function (CLcr, >80 mL/min). DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium sparing drugs during the study, individual mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs.

Drug Interactions:

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see Metabolism). In *in vitro* studies, DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3mg DRSP for 14 days did not affect the systemic clearance of the CYP2C19 substrate omeprazole (40 mg) and the CYP2C19 product 5-hydroxy-omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrated that DRSP did not inhibit CYP2C19 and CYP3A4 in vivo.

Two further clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4, were each performed in 24 healthy, postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady-state DRSP concentrations achieved after administration of 3 mg DRSP/day.

Based on the available results of *in vivo* and *in vitro* studies, it can be concluded that, at clinical dose level, DRSP is unlikely to interact significantly with cytochrome P450 enzymes.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Co-Administration with Drugs that Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking drospirenone with other drugs that may affect electrolytes, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or non-steroidal anti-inflammatory drugs (NSAIDs).

Electrolytes were studied in 230 postmenopausal women with hypertension and/or diabetes mellitus requiring an ACE inhibitor or angiotensin receptor blocker (ARB). Of these, 26 patients had a creatinine clearance >50 mL/min to <80 mL/min. Patients were given 1 mg estradiol (E2) and 3 mg drospirenone (DRSP) (n=112) or placebo (n=118) over 28 days. Non-diabetic patients also received ibuprofen 1200 mg/day for 5 days during the study. There was a single case of serum potassium >6.0 mEq/L and a single case of serum sodium <130 mEq/L on treatment, both occurring following five days of ibuprofen therapy in two women taking E2/DRSP. Serum potassium levels ≥5.5 mEq/L were observed in 8 (7.3%) E2/DRSP-treated subjects (3 diabetic and 5 nondiabetic) and in 3 (2.6%) placebo-treated subjects (2 diabetic and 1 nondiabetic). After 28 days of exposure, the mean change from baseline in serum potassium was 0.11 mEq/L for the E2/DRSP group and 0.08 mEq/L for the placebo group. None of the subjects with serum potassium levels ≥5.5 mEq/L had cardiovascular adverse events. A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was

performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium Cmax and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

Of note, occasional or chronic use of NSAID medication was not restricted in any of the ANGELIQ clinical trials.

Clinical Studies

Support for the indications: Support for treatment of vasomotor symptoms and vaginal and vulvar atrophy was shown through bioequivalence of the E2 component of the combination product with a currently marketed E2 product (Estrace®). The multiple-dose bioequivalence study evaluated the bioequivalence of E2 from a tablet containing DRSP (2 mg) and E2 (1 mg) relative to Estrace (1 mg) tablet. DRSP/E2 tablets met the criteria for bioequivalence to Estrace.

Effects on Endometrium: In a one year clinical trial of 1,142 postmenopausal subjects treated with E2 alone or E2 + 0.5, 1, 2, or 3 mg DRSP, endometrial biopsies were performed on 966 (84.6%) subjects during the treatment period. Eight subjects in the E2 monotherapy group developed endometrial hyperplasia (4 simple hyperplasia with no cytological atypia, 3 complex hyperplasia with no cytological atypia, and 1 complex hyperplasia with cytological atypia), and one subject in the 1 mg E2 + 2 mg DRSP group developed simple hyperplasia with no cytological atypia. Table 2 shows that there were no diagnoses of endometrial hyperplasia in the **ANGELIQ** group.

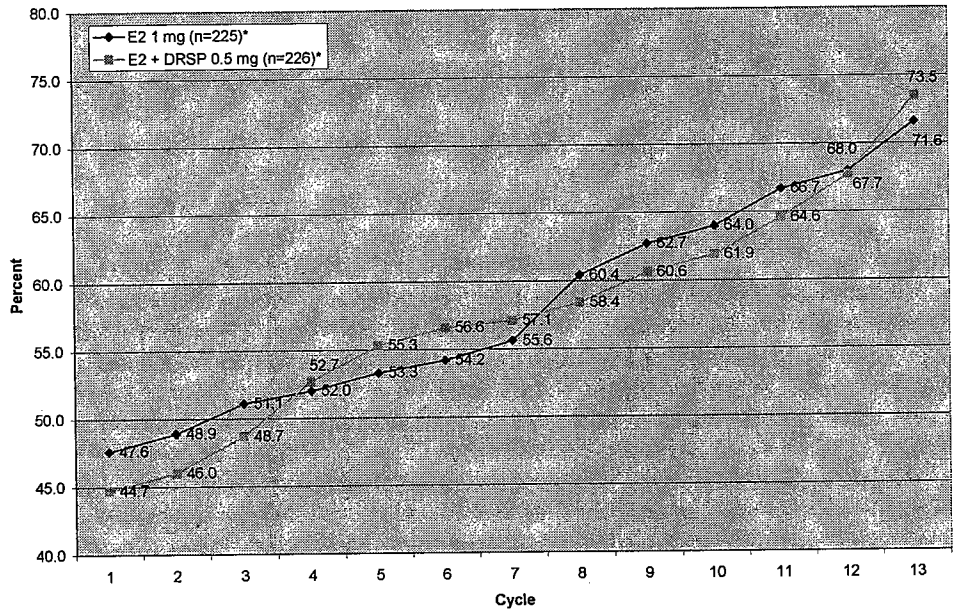
Table 2. Incidence of Endometrial Hyperplasia after up to 12 Months of Treatment

	E2 1 mg	**ANGELIQ**
Total No. Subjects	226	227
Total No. of On-Treatment Biopsies	197 (87.2%)	191 (84.1%)
Hyperplasia	8 (4.0%)	0 (0%)

Effects on Uterine Bleeding or Spotting:

In a cumulative analysis performed over 12 months in a double blind trial, the proportions of women with amenorrhea increased and at one year, 73.5% of subjects on **ANGELIQ** had amenorrhea. Results are shown in Figure 2.

Figure 2. Cumulative proportion of subjects with amenorrhea at a given cycle through cycle 13, LOCF



* One patient from each treatment group did not have bleeding diary information

Women's Health Initiative Studies: The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of 0.625 mg conjugated equine estrogens (CE) per day alone or the use of 0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "'global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The CE/MPA sub-study was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index". Results of the CE/MPA sub-study, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 3 below:

Table 3. Relative and Absolute Risk Seen in the CE/MPA Substudy of WHI[a]			
Event[c]	Relative Risk CE/MPA vs placebo at 5.2 Years (95% CI*)	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis [d]	2.07 (1.49-2.87)	13	26
Vertebral fractures [d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures [d]	0.77 (0.69-0.86)	170	131

[a] adapted from JAMA, 2002; 288:321-333

[b] includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

[c] a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

[d] not included in Global Index

* nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," absolute excess risks per 10,000 person-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures.